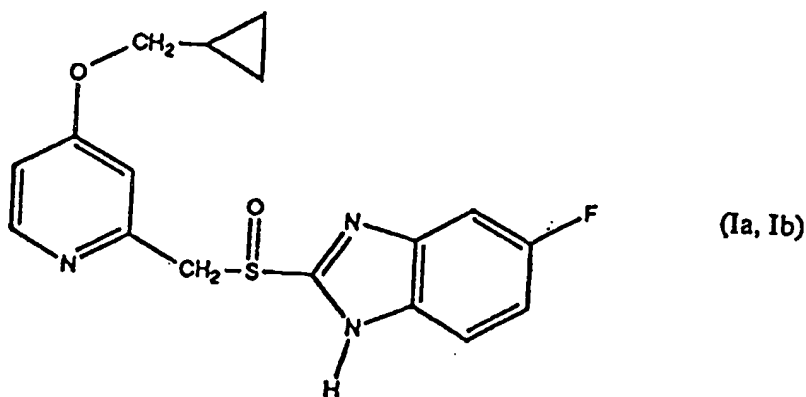




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(54) Title: NOVEL SUBSTITUTED BENZIMIDAZOLES



## (57) Abstract

The novel optically pure compounds, i.e. the single enantiomeric compounds (1a, 1b), (+)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a therapeutically acceptable salt thereof, such as Na<sup>+</sup>, Mg<sup>2+</sup>, Li<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and N<sup>+</sup>(R)<sub>4</sub> salts, where R is an alkyl group with 1-4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

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## NOVEL SUBSTITUTED BENZIMIDAZOLES

Field of the invention

- 5 The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

10

Background of the invention

- The compound 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, and therapeutically acceptable salts thereof are described in  
15 US-A 5 008 278 corresponding to EP 90901079.5. This compound and its therapeutically acceptable salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved  
20 pharmacokinetic and metabolic properties which will give an improved therapeutic profile. The present invention provides such compounds, which are novel salts of single enantiomers of 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as well as the novel single enantiomers of the neutral form of said compound.

25

- The separation of the enantiomers of therapeutically active sulfoxides, such as substituted benzimidazoles, for example omeprazole (5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole) in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19. The isolation of single  
30 enantiomers of the sulfoxide agent Ro 18-5364 is described in Euro. J. Biochem. 166 (1987) 453-459. Furthermore, separation of the enantiomers of omeprazole in a preparative scale is described in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group,  
35 the active compound, omeprazole, is quite sensitive and the acid has to be quickly

neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values  
5 between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralization will create heat which will be difficult to handle in large scale production.

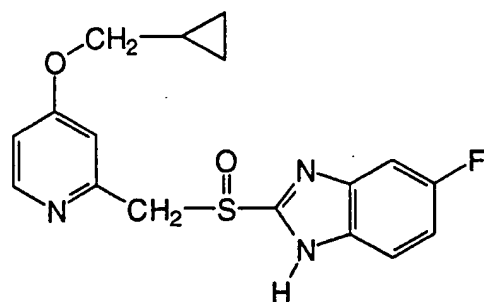
The present invention in a further aspect provides a novel method for preparing  
10 the novel compounds of the invention in large scale. Thus, this novel method can be used in large scale to obtain single enantiomers of the compound of the invention in neutral form, as well as in the form of the therapeutically acceptable salts.

15 These novel compounds of the invention, being sulfoxides, could be expected to undergo racemization in neutral pH as well as in basic pH. See for example Brändström et al. Acta Chemica Scandinavica 43 (1989) p. 536-547. Surprisingly, the inventors now found that the novel single enantiomers of 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole as well as its  
20 therapeutically acceptable salts are stable towards racemization.

There is no example known in the prior art of any isolated or characterized single enantiomers of the compound of the invention. Furthermore, the inventors are not aware of any description in the scientific literature of any isolated salt of a single  
25 enantiomer of the claimed type.

#### Detailed description of the invention

30 The present invention refers to the new single enantiomers of 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole according to compounds Ia and Ib



(Ia, Ib)

Ia (+)-enantiomer

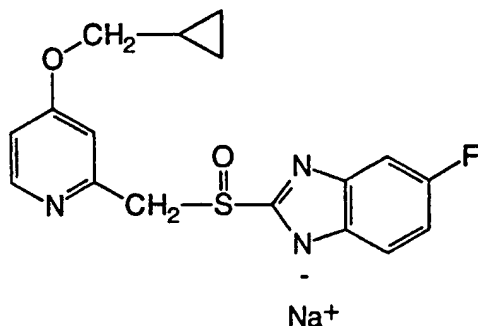
Ib (-)-enantiomer

- 5 as well as therapeutically acceptable salts thereof. Such salts are for example the  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Li}^+$ ,  $\text{K}^+$  and  $\text{N}^+(\text{R})_4$  salts of the single enantiomers of said compound, where R is an alkyl group with 1-4 carbon atoms, i.e. (+)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole
- 10 as well as  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Li}^+$ ,  $\text{K}^+$  and  $\text{N}^+(\text{R})_4$  salts of the single enantiomers, where R is an alkyl group with 1-4 carbon atoms.

- Particularly preferred salts of the compound of the invention are the  $\text{Na}^+$ ,  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$  salts of the single enantiomers of 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.
- 15

The most preferred compounds of the invention are the optically pure  $\text{Na}^+$  salts of 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole according to compounds IIa and IIb

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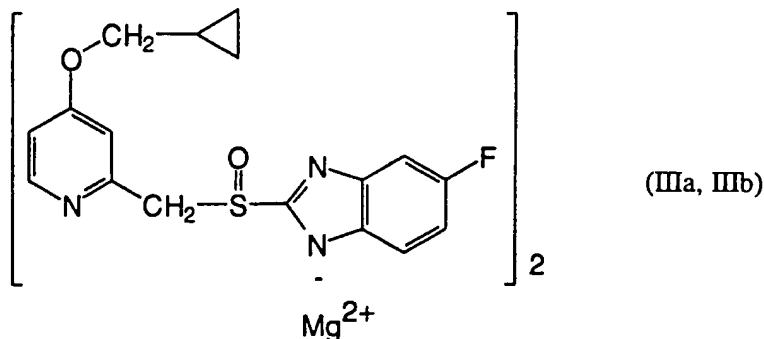


(IIa, IIb)

IIa (+)-enantiomer

IIb (-)-enantiomer

and the optically pure magnesium salts of said compounds having the formulas IIIa and IIIb.



5

IIIa (+)-enantiomer

IIIb (-)-enantiomer

With the expression "optically pure compound of the invention" is meant the (+)-  
 10 enantiomer of said compound essentially free from the corresponding (-)-  
 enantiomer and the (-)-enantiomer essentially free from the corresponding (+)-  
 enantiomer, respectively. Thus, every single compound of the invention is  
 obtained in high optical purity. By means of the novel specific method according  
 to one aspect of the invention of preparing the single enantiomers, the compounds  
 15 of the invention are easy to obtain. Moreover, as mentioned above, the novel  
 optically pure compounds are stable towards racemization in neutral pH as well  
 as basic pH. The former was surprising since the mechanism of the degradation  
 reactions at neutral pH of these kind of sulfoxides (omeprazole analogues)  
 contains reversible reactions via achiral intermediates (see *e.g.* Brändström *et al.*  
 20 *Acta Chemica Scandinavica* 43 (1989) p.536-547, especially p.538). It is obvious that  
 such reversible reactions from achiral intermediates back to a sulfoxide would  
 cause a racemic product. Further, the novel optically pure compounds are stable  
 towards racemization in basic pH, which was surprising since the known  
 deprotonation at the carbon atom between the pyridine ring and the chiral  
 25 sulphur atom was expected to cause racemization under alkaline conditions. This  
 high stability towards racemization, both in neutral pH and basic pH, makes it  
 possible to use a single enantiomeric compound of the invention in the neutral  
 form as well as salts thereof in therapy.

The specific method of preparation of the single enantiomers of the compound of the invention is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomeric compounds in the neutral form as well as the salts thereof.

5

The single enantiomeric compounds of the invention as well as the racemate show exceedingly high bioavailability, and still said compounds are very effective as inhibitors of gastric acid secretion and exhibit a high chemical stability in solution at a neutral pH.

10

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the single enantiomeric compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. Further, the compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may be also useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

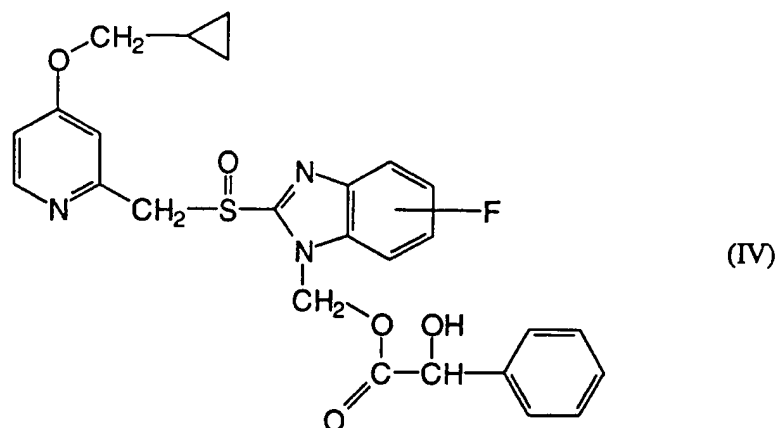
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Yet a further aspect of the invention is the diastereomeric mixture of a regioisomeric mixture having the formula IV, which is an intermediate used in the specific method of preparation, wherein the fluoro substituent in the benzimidazole moiety is in position 5 or 6.

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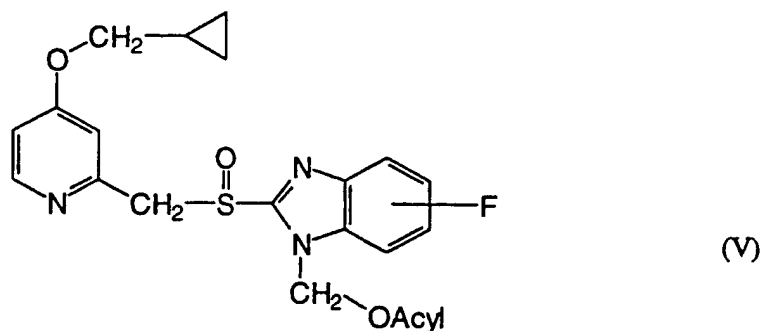


### Preparation

5

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the stereoisomers of a diastereomeric mixture of the regioisomeric mixture of the following type, 5- and 6-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-acyloxymethyl]-1H-benzimidazole, formula V

10



wherein the fluoro substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomeric compounds of the invention in neutral form are then isolated by neutralizing aqueous solutions of the salts of said compounds with a neutralizing agent which can be an acid or an ester such as methyl formate.

20



The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

- 5 The diastereomeric esters can be separated either by chromatography or fractional crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water; or with a base in a mixture of acetonitrile and water, but the acyl  
10 group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be  $\text{OH}^-$  or  $\text{R}^1\text{O}^-$  where  $\text{R}^1$  can be any alkyl or aryl group.

To obtain the optically pure  $\text{Na}^+$  salts of the invention, i.e.  $\text{Na}^+$  salts of the single  
15 enantiomeric compound of the invention, the resulting compound in neutral form is treated with a base, such as  $\text{NaOH}$ , in an aqueous or nonaqueous medium, or with  $\text{NaOR}^2$  wherein  $\text{R}^2$  is an alkyl group containing 1-4 carbon atoms, or with  $\text{NaNH}_2$ . Also alkaline salts wherein the cation is  $\text{Li}^+$  or  $\text{K}^+$  may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the  
20 crystalline form of the single enantiomers of the  $\text{Na}^+$  salts, to the optically pure amorphous powder of the  $\text{Na}^+$  salt are added a mixture of 2-butanone and toluene. The crystalline form of the single enantiomers of the  $\text{Na}^+$  salt may also be prepared by adding  $\text{NaOH}$  to a mixture of the single enantiomeric compound of invention in neutral form and a non-aqueous medium, such as a mixture of 2-  
25 butanone and toluene.

To obtain the optically pure  $\text{Mg}^{2+}$  salts of the invention, the optically pure compound of the invention in the neutral form is treated with a base, such as  
30  $\text{Mg}(\text{OR}^3)_2$ , wherein  $\text{R}^3$  is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g.  $\text{ROH}$ , or in an ether such as tetrahydrofuran. The optically pure  $\text{Mg}^{2+}$  salts may also be prepared by treating single enantiomeric compound of the invention as a sodium salt with an aqueous solution of an inorganic magnesium salt such as  $\text{MgCl}_2$ , whereupon the  $\text{Mg}^{2+}$  salts are precipitated. In an analogous way, also alkaline salts wherein the  
35 cation is  $\text{Ca}^{2+}$  can be prepared, using an aqueous solution of an inorganic calcium salt such as  $\text{CaCl}_2$ .

Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds IIa and IIb) and the magnesium salts (compound IIIa and IIIb), exemplified by their salts with  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and  $\text{N}^+(\text{R})_4$ , where R is an alkyl group with 1-4 C-atoms.

5

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a  
10 pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral  
15 administration. An active compound in a form with high solubility in water is requested for a parenteral preparation, for some oral preparations an active compound in a form with low solubility is suitable.

In the preparation of pharmaceutical formulations in form of dosage units for oral  
20 administration the pure enantiomeric compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating  
25 agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among  
30 pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

35

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

- 5 Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatin. The capsules may be enteric-coated as described above.
- 10 Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable
- 15 vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.
- 20 Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring
- 25 agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.
- 30 Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral
- 35 administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

5

The invention is illustrated by the following examples.

Example 1. Preparation of (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

10

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (5.0 g, 9.8 mmol) were divided into five parts and each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereo isomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (67.5/32.5). However each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their solutions during the hydrolysis step. To the acetonitrile/aqueous solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH<sub>4</sub>Cl whereupon the solutions from each preparation were combined and extracted with methylene chloride. The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed by film evaporation. Addition of 30 ml of acetonitrile afforded the product to crystallize and after filtration there was obtained 260 mg (16%) of the title compound as white crystals, m.p. 152°-154°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was 99.2%. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +208.6° (c=0.5%, chloroform).

30

NMR data are given below.

Example 2. Preparation of (-)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

To the acetonitrile/aqueous solutions of the less lipophilic diastereomer of 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (obtained from the very same reversed phase chromatographic preparations described in Example 1) were added 1.0 M NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH<sub>4</sub>Cl. The solutions from each preparation were combined and extracted with methylene chloride. The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed by film evaporation. Addition of 50 ml of acetonitrile afforded the product to crystallize and after filtration there was obtained 460 mg (28%) of the title compound as white crystals, m.p. 152°-154°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was 99.0%.  $[\alpha]^{20}_D = -208.7^\circ$  (c=0.5%, chloroform).

NMR data are given below.

Example 3. Preparation of freeze-dried (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a methylene chloride solution (5 ml) of (-)-5-fluoro-2-[[[4-cyclopropyl-methoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (100 mg, 0.29 mmol) was added an aqueous solution of 0.2 M NaOH (1.4 ml, 0.28 mmol). The mixture was stirred for 30 minutes and then the layers were separated. The aqueous phase was freeze-dried which afforded 83 mg (78%) of the product as a white amorphous powder.  $[\alpha]^{20}_D = +47.2^\circ$  (c=1.0%, water).

NMR data are given below

Example 4. Preparation of (+)-5-fluoro-2-[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in the crystalline form

Freeze-dried (+)-5-fluoro-2-[[4-cyclopropyl-methoxy-2-pyridinyl)-methyl]sulfinyl]-1-H-benzimidazole sodium salt (61 mg) obtained in Example 3 was dissolved in 2-butanone (1 ml). Toluene (2 ml) was added slowly while stirring and white crystals were precipitated. The product was filtered off and washed with a small amount of diethyl ether. There was obtained 50 mg (82%) of the title compound as a crystalline product. m.p. (decomposition) 230°-240°C.

NMR data are given below

Example 5. Preparation of freeze-dried (-)-5-fluoro-2-[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a methylene chloride solution (5 ml) of (+)-5-fluoro-2-[[4-cyclopropylmethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (100 mg, 0.29 mmol) was added an aqueous solution of 0.2 M NaOH (1.4 ml, 0.28 mmol). The mixture was stirred for 30 minutes and then the layers were separated. The aqueous phase was freeze-dried which afforded 89 mg (84%) of the product as a white amorphous powder.  $[\alpha]_D^{20} = -46.4^\circ$  (c=1.0%, water).

NMR data are given below

Example 6. Preparation of (-)-5-fluoro-2-[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in the crystalline form

Freeze-dried (-)-5-fluoro-2-[[4-cyclopropyl-methoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole sodium salt (75 mg) obtained in Example 5 was dissolved in 2-butanone (1 ml). Toluene (2 ml) was added slowly while stirring and white crystals were precipitated. The product was filtered off and washed with a small amount of diethyl ether. There was obtained 60 mg (82%) of the title compound as a crystalline product. m.p. (decomposition) 230°-240°C.

NMR data are given below

Example 7. Preparation of (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

Magnesium (7.1 mg, 0.29 mmol) was dissolved and reacted with methanol at 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after two hours. (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.58 mmol) was added after the magnesium methoxide solution had been chilled to room temperature. The mixture was stirred for two hours whereupon a small amount of water (0.05 ml) was added. After stirring another hour the small amount of inorganic salts were filtered off. The solution was concentrated on a rotavapor until two ml of the solution was left. While chilling and stirring, water was added dropwise which afforded the product to precipitate. After filtration the product was washed with a small amount of water and then dried in vacuum. There was obtained 97 mg (47%) of the title compound as a white powder.  $[\alpha]^{20}_D = +191.3^\circ$  (c=1.0%, DMSO).

Example 8. Preparation of (-)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

Magnesium (7.1 mg, 0.29 mmol) was dissolved and reacted with methanol at 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after two hours. (-)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.58 mmol) was added after the magnesium methoxide solution had been chilled to room temperature. The mixture was stirred for two hours whereupon a small amount of water (0.05 ml) was added. After stirring another hour the small amount of inorganic salts were filtered off. The solution was concentrated on a rotavapor until two ml of the solution was left. While chilling and stirring, water was added dropwise which afforded the product to precipitate. After filtration the product was washed with a small amount of water and then dried in vacuum. There was obtained 84 mg (41%) of the title compound as a white powder. The optical rotation was determined as (-). Due to difficulties of dissolving the compound in a number of solvents a representative value of optical rotation was not obtained.

Table 1.

	<u>Ex.</u>	<u>Solvent</u>	<u>NMR data d ppm</u>
5	1.	DMSO-d <sub>6</sub> 500 MHz	0.25 (m, 2H), 0.53 (m, 2H), 1.13 (m, 1H), 3.67 (m, 1H), 3.73 (m, 1H), 4.59 (d, 1H), 4.69 (d, 1H), 6.76 (d, 1H), 6.88 (dd, 1H), 7.17 (m, 1H), 7.43 (m, 1H), 7.65 (m, 1H), 8.28 (d, 1H), ≈13 (b, 1H).
10	2.	DMSO-d <sub>6</sub> 500 MHz	0.25 (m, 2H), 0.53 (m, 2H), 1.13 (m, 1H), 3.68 (m, 1H), 3.73 (m, 1H), 4.59 (d, 1H), 4.69 (d, 1H), 6.76 (d, 1H), 6.88 (dd, 1H), 7.17 (m, 1H), 7.43 (m, 1H), 7.64 (m, 1H), 8.28 (d, 1H). ≈13 (b, 1H).
15	3.	DMSO-d <sub>6</sub> 500 MHz	0.21 (m, 2H), 0.50 (m, 2H), 1.08 (m, 1H), 3.46 (m, 1H), 3.62 (m, 1H), 4.40 (d, 1H), 4.56 (d, 1H), 6.57 (d, 1H), 6.71 (m, 1H), 6.81 (m, 1H), 7.15 (dd, 1H), 7.41 (m, 1H), 8.30 (d, 1H).
20	4.	DMSO-d <sub>6</sub> 300 MHz	0.22 (m, 2H), 0.50 (m, 2H), 1.07 (m, 1H), 3.50 (m, 1H), 3.66 (m, 1H), 4.41 (d, 1H), 4.62 (d, 1H), 6.59 (d, 1H), 6.69 (m, 1H), 6.78 (m, 1H), 7.13 (dd, 1H), 7.39 (m, 1H), 8.29 (d, 1H).
25	5.	DMSO-d <sub>6</sub> 500 MHz	0.22 (m, 2H), 0.50 (m, 2H), 1.08 (m, 1H), 3.46 (m, 1H), 3.62 (m, 1H), 4.40 (d, 1H), 4.56 (d, 1H), 6.57 (d, 1H), 6.71 (m, 1H), 6.80 (m, 1H), 7.15 (dd, 1H), 7.40 (m, 1H), 8.30 (d, 1H).
30	6.	DMSO-d <sub>6</sub> 300 MHz	0.22 (m, 2H), 0.50 (m, 2H), 1.07 (m, 1H), 3.51 (m, 1H), 3.66 (m, 1H), 4.41 (d, 1H), 4.62 (d, 1H), 6.60 (d, 1H), 6.69 (m, 1H), 6.78 (m, 1H), 7.13 (dd, 1H), 7.39 (m, 1H), 8.29 (d, 1H).

35

Preparation of the synthetic intermediate according to the invention will be described in the following example.



Example 9. Preparation of 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

5

A solution of 1.6 g (40 mmol) sodium hydroxide in 8 ml water was added to a mixture of 6.8 g (20 mmol) tetrabutylammonium hydrogen sulfate and 3.0 g (20 mmol) of (R)-(-)-mandelic acid. Chloroform (200 ml) and a mixture of 5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1-(chloromethyl)-1H-benzimidazole and 6-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1-(chloromethyl)-1H-benzimidazole (as racemates) were added and the mixture was refluxed for one hour. The reaction mixture was chilled and then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of solvents yielded a diastereomeric mixture of the two regioisomeric mandelic esters. The crude product was used directly in the chromatographic step where the diastereomers were separated (Example 1 and 2). Yield: 9.0 g, 88%.

NMR data are given below.

20

Table 2.

<u>Ex.</u>	<u>Solvent</u>	<u>NMR data d ppm</u>
25 9.	CDCl <sub>3</sub>	0.3-0.4 (m, 2H), 0.6-0.7 (m, 2H), 1.1-1.3 (m, 1H), 3.7-3.9 (m, 2H), 4.6-4.9 (m, 2H), 5.2-5.3 (m, 1H), 6.2-6.6 (m, 2H), ≈6.7 (m, 1H), 6.85 (m, 1H), 7.0-7.8 (m, 8H), 8.1-8.2 (m, 1H).

30

The best mode of carrying out the invention known at present is to use the magnesium salts of the optically pure compounds of the invention, thus the compounds described in Examples 7 and 8.

35 Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

5	Compound according to Example 4	1.0 g
	Sugar, powder	30.0 g
	Saccharine	0.6 g
	Glycerol	5.0 g
10	Flavouring agent	0.05 g
	Ethanol 96%	5.0 g
	Distilled water q.s. to a final volume of	100 ml

15 Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

20

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

25	I Compound according to Example 7	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
30	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
	II Cellulose acetate phthalate	200 g
35	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

- I Compound according to Example 7, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tableting machine using 7 mm diameter punches.
- 10 II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota<sup>R</sup>, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

15

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 6	4 g
20 Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

25

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

30

Compound according to Example 4	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
35 Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

- 5 500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

10	Hydroxypropyl methylcellulose phthalate	70 g
	Cetyl alcohol	4 g
	Acetone	200 g
	Ethanol	600 g

15

The final coated pellets were filled into capsules.

#### Suppositories

- 20 Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 4	4 g
Witepsol H-15	180 g

25

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

30

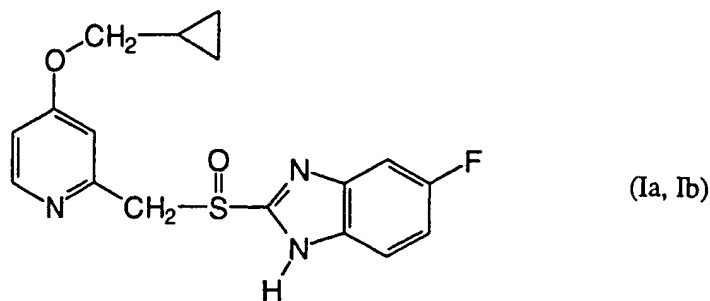
#### Stability towards racemization at different pH:es

- 35 The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations ( $10^{-5}$  M) at 37°C in aqueous buffer solutions at pH 7 and pH 11. The stereo chemical stability was measured by comparing the optical purity for the (+)-isomer of 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole in buffer

solution immediately after dissolving and after several hours. The surprising high stereo chemical stability in neutral as well as in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained neither at pH 7 nor at pH 11, even after 28 hours. At pH 5 7, however, the chemical degradation of the compounds are much apparent after 28 hours.

Claims

1. Single enantiomeric compounds having the formula Ia and Ib



Ia (+)-enantiomer

Ib (-)-enantiomer

and the therapeutically acceptable salts thereof.

2. Compounds according to claim 1 characterized in that the compound is (+)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a therapeutically acceptable salt thereof, substantially free of its (-)-enantiomer.

3. Compounds according to claim 1 characterized in that the compound is (-)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, or a therapeutically acceptable salt thereof, substantially free of its (+)-enantiomer.

4. Compounds according to any of claims 1-3 characterized in that the therapeutically acceptable salts are Na<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>, Li<sup>+</sup>, K<sup>+</sup> and N<sup>+</sup>(R)<sub>4</sub> salts wherein R is an alkyl group with 1-4 carbon atoms.

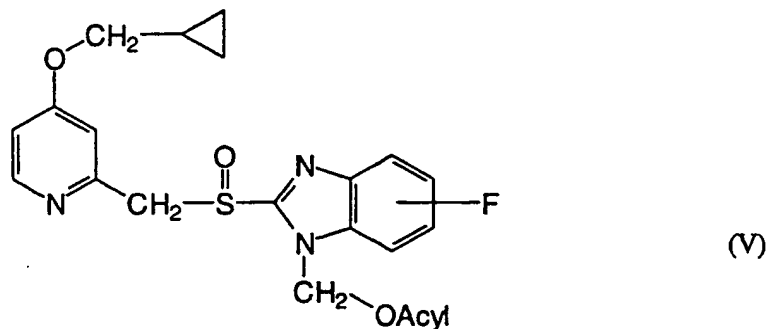
5. Compounds according to any of claims 1-4 characterized in that the compounds are (+)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

6. Compounds according to any of claims 1-5 characterized in that the compounds are (+)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt or magnesium salt and (-)-5-fluoro-2-[[[(4-cyclopropyl-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt or magnesium salt in their crystalline forms.

7. Compounds according to claims 1 and 2 characterized in that the compound is (+)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt or magnesium salt, respectively, in its crystalline form substantially free of its (-)-enantiomer.

8. Compounds according to claims 1 and 3 characterized in that the compound is (-)-5-fluoro-2-[[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt or magnesium salt, respectively, in its crystalline form substantially free of its (+)-enantiomer.

9. Process for the preparation of a compound according to claim 1 characterized in that a diastereomeric ester of formula V



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wherein the fluoro substituent in the benzimidazole moiety is in position 5 or 6, and wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is subjected to solvolysis with an alkaline solution where the acyloxymethyl group is hydrolyzed off giving the enantiomeric compound in neutral form after neutralization with a neutralizing agent whereupon the enantiomeric compound in neutral form optionally is converted to a therapeutically salt.

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10. Process according to claim 9 characterized in that the diastereomers are separated by chromatography or fractional crystallization.
11. Process according to claim 9 characterized in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide; or a base in a mixture of protic and aprotic solvents, such as water and acetonitrile.
12. Process for the preparation of a compound according to any of claims 1-4 in crystalline form characterized in that a product obtained in claim 9 either in neutral form or in the form of a therapeutically salt is treated with a non-aqueous solvent to precipitate the product.
13. Process for preparation of (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt and (-)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt in their crystalline forms characterized in that (+)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt and (-)-5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt crude product respectively is treated with a non-aqueous medium, such as 2-butanone and toluene.
14. Pharmaceutical preparation comprising a single enantiomeric compound according to any of claims 1-8 as active ingredient.
15. Single enantiomeric compounds according to any of claims 1-8 for use in therapy.
16. Use of a single enantiomeric compound according to any of claims 1-8 in the manufacture of a pharmaceutical formulation for inhibiting gastric acid secretion.
17. Use of a single enantiomeric compound according to any of claims 1-8 for the manufacture of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.



18. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.
- 5 19. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.
- 10 20. The compounds 5-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1-[mandeloyloxymethyl]-1H-benzimidazole and 6-fluoro-2-[[[4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1-[mandeloyloxymethyl]-1H-benzimidazole.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00518

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	US 5008278 A (A.E. BRÄNDSTRÖM ET AL), 16 April 1991 (16.04.91) --	1-15,20
Y	DE 4035455 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 14 May 1992 (14.05.92) -- -----	9-13,20

☐ Further documents are listed in the continuation of Box C.
 ☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

6 Sept 1995

Date of mailing of the international search report

19 -09- 1995

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00518

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by therapy,  
see Rule 39.1.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/95

International application No.

PCT/SE 95/00518

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US-A-	5008278	16/04/91	AT-T- 110723	15/09/94
			AU-B- 634741	04/03/93
			AU-B- 639429	29/07/93
			AU-A- 4813290	10/07/90
			AU-A- 4817590	10/07/90
			BG-A- 60101	15/10/93
			BG-A- 60102	15/10/93
			CA-A- 2005980	22/06/90
			CA-A- 2005986	22/06/90
			CN-B- 1028231	19/04/95
			CN-B- 1028233	19/04/95
			CN-A- 1043937	18/07/90
			DE-D, T- 68917937	05/01/95
			EG-A- 19302	30/11/94
			EG-A- 19303	30/11/94
			EP-A, B- 0449935	09/10/91
			SE-T3- 0449935	
			EP-A- 0449940	09/10/91
			GR-B- 1000316	25/06/92
			GR-A- 89100838	15/03/91
			IL-A- 92799	25/01/94
			SE-A- 8804629	22/12/88
			US-A- 5025024	18/06/91
			US-A- 5039808	13/08/91
			WO-A- 9006924	28/06/90
			WO-A- 9006925	28/06/90
DE-A1-	4035455	14/05/92	AU-A- 8840691	11/06/92
			WO-A- 9208716	29/05/92